

## **REMARKS**

### Withdrawn Rejections

Applicant notes that the Office has found Applicant's arguments submitted on May 31, 2005 to be persuasive. Applicant thanks the Examiner for withdrawing the previous rejections.

### Claim Rejections - 35 U.S.C. § 103(a)

(1) Claims 1-34 and 67-100 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over *Baldarelli et al.* (U.S. Patent No. 6,015,714, issued Jan. 18, 2000, hereinafter "*Baldarelli*") in view of *Kool* (U.S. Patent No. 5,714,320, issued Feb. 3, 1998, hereinafter "*Kool*"). Applicant respectfully traverses this rejection.

#### **(a) Claim 1**

The combination of *Baldarelli* and *Kool* does not render claim 1 obvious. First, Applicant respectfully asserts that the proposed combination is improper. It has been well established that teachings of references can be combined only if there is some suggestion or incentive in the references to do so. *See, e.g., ACS Hosp. Sys., Inc. v. Montefiore Hosp.*, 732 F.2d 1572, 1577, 221 U.S.P.Q. 929, 933 (Fed. Cir. 1984). Accordingly, there must be a teaching in the relevant art which would suggest to a person having ordinary skill in that art the desirability of combining the nucleic acid sequencing method of *Baldarelli* with a "circular template" nucleic acid synthesis of *Kool*. There is no teaching in either reference that would suggest the desirability of combining them and, further, knowledge generally available in the art would not motivate one to combine the references. Neither of the references suggest any advantage or benefit for combining the technologies of the two disclosures. Here, the Office has used impermissible hindsight analysis and, with the invention of the claims in mind, have picked two isolated disclosures in the art and attempted to combine them when there is no motivation to do so. *See In re Fine* 837 F.2d 1071, 1075, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988). Therefore, for at least this reason alone, claim 1 is not rendered obvious by the cited combination of *Baldarelli* and *Kool*.

Second, irrespective of the clear lack of motivation to combine the *Baldarelli* and *Kool* references, the rejection is improper because, even if the teachings of the two references are properly combinable, such combination does not result in Applicant's claimed invention.

Independent claim 1 recites the following:

1. A method of sequencing a nucleic acid molecule comprising steps of:  
providing two separate, adjacent pools of a medium and an interface between the two pools, the interface having a channel so dimensioned as to allow sequential nucleotide-by-nucleotide passage from one pool to the other pool of only one nucleic acid molecule at a time;  
providing a nucleic acid molecule ***with at least one repeat of a nucleotide sequence to be determined***, wherein the nucleic acid molecule is enzymatically synthesized using a circular template, and ***wherein the nucleic acid molecule contains modified nucleotides that reduce secondary structure in the nucleic acid molecule***;  
placing the nucleic acid molecule in one of the two pools; and  
taking measurements as each of the nucleotides of the nucleic acid molecule passes through the channel so as to determine the sequence of the nucleic acid molecule.

(Emphasis added). The combination of *Baldarelli* and *Kool* does not teach or suggest all of the elements of claim 1 such as, for example, the features highlighted in claim 1 above. There are several deficiencies of *Baldarelli* with respect to rendering independent claim 1 obvious, other than the ones admitted by the Office as follows:

Baldarelli et al. do not disclose using a circular template, the nucleic acid molecule containing modified nucleotides, which are modified adenosine, modified thymine, modified guanosine and modified cytosine.

*Office Action* at 3. The deficiencies noted above are not remedied by combining *Baldarelli* with *Kool*. In addition to the deficiencies noted by the Office, *Baldarelli* does not disclose or suggest the feature of “at least one repeat of a nucleotide sequence to be determined,” as recited in claim 1.

Applicants have noted in the specification at paragraph [0008] that it is advantageous to perform nanopore sequencing using a template comprising multiple copies of a nucleic acid of interest. *Baldarelli* states that “[i]ndividual molecules in a population may be characterized in rapid succession.” *Baldarelli* at col. 1, lines 43-45. *Baldarelli* does not teach or suggest that it would be desirable to sequence a molecule that contained multiple amplified copies of a single nucleic acid of interest. In anything, *Baldarelli* teaches away from doing so, since it indicates that its method is rapid. Other factors being equal, sequencing a template that contains multiple copies of a nucleic acid of interest would be expected to take longer than sequencing a template containing only a single copy of the nucleic acid of interest. The Office provides not evidence

that *Kool* remedies this deficiency of *Baldarelli*. Nothing in *Kool* teaches or suggests the feature of “at least one repeat of a nucleotide sequence to be determined,” as recited in claim 1. Therefore, for at least this reason alone, claim 1 is not obvious in view of the combination of *Baldarelli* and *Kool*.

In addition, neither *Baldarelli* nor *Kool* teach or suggest the feature of “modified nucleotides that reduce secondary structure in the nucleic acid molecule,” as recited in claim 1. The Office admits that “the modified nucleotide used in the method of Kool et al. is to make cleavage site..., while in the instant invention, the modified nucleotide of the synthesized nucleic acid is to reduce secondary structures in the synthesized nucleic acid.” *Office Action* at 3. The Office appears to suggest that there is motivation to use the modified nucleotides disclosed by *Kool* in alleging that the elements used in the synthesis of nucleic acid are the same. Applicants respectfully disagree. *Kool* discloses, “[t]his nonnatural nucleotide contains synthetic modifications which allow it to be cleaved selectively....” *Col.* 30, lines 65-66. Indeed, the teaching of *Kool* teaches away from incorporating nucleotides that contain synthetic modifications when it is desired to determine the sequence the nucleic acid sequence. The inventor has discovered, however, that providing modified nucleotides that reduce secondary structure improves the claimed method of determining the sequence of the nucleic acid. Contrary to the assertion by the Office, the elements are not necessarily the same. For example, claims 31, 74, 76, 77 provide for a modified thymidine, which is not taught or suggested by *Kool*. Therefore, a modified nucleotide that reduces secondary structures, as recited in claim 1, is not necessarily the same as a modified nucleotide that allows selective cleavage, as disclosed by *Kool*. Therefore, for at least this reason alone, claim 1 is not obvious in view of the combination of *Baldarelli* and *Kool*.

For each of the individual reasons listed above, Applicant respectfully requests that the rejection of claim 1 be withdrawn.

**(b) Claims 2-34**

Because independent claim 1 is allowable over the prior art of record, its dependent claims 2-34 are allowable as a matter of law, for at least the reason that these dependent claims contain all features/steps of their respective independent claim 1. *In re Fine*, 837 F.2d 1071, 5 U.S.P.Q.2d

1596 (Fed. Cir. 1988). Additionally and notwithstanding the foregoing allowability of the independent claim 1, the dependent claims recite further features and/or combinations of features (as is apparent by examination of the claims themselves) that are patentably distinct from the prior art of record. Hence, there are other reasons why the dependent claims are allowable.

Specifically, Applicant requests that the Office point to where the features of each individual dependent claim are found in the references. There are numerous features in dependent claims 2-34 that are not discussed in the Office Action. By way of example, claim 5 recites “wherein the nucleic acid is an unstructured nucleic acid.” The references, even if combined do not teach or suggest this feature. By way of further example, claim 34 recites “wherein the nucleic acid contains 2-aminoadenosine, and 2-thiothymidine.” The references, even if combined do not teach or suggest this feature. Thus, the Office Action has not established a *prima facie* case of obviousness with respect to each of the dependent claims 2-34. Applicant respectfully requests that the rejection of the claims be withdrawn.

**(c) Claim 67**

Independent claim 67 recites the following:

67. A method of sequencing a nucleic acid molecule comprising steps of:  
providing two separate, adjacent pools of a medium and an interface between the two pools, the interface having a channel so dimensioned as to allow sequential nucleotide-by-nucleotide passage from one pool to the other pool of only one nucleic acid molecule at a time;  
***providing a nucleic acid molecule with modified nucleotides that reduce secondary structure in the nucleic acid molecule;***  
placing the nucleic acid molecule in one of the two pools; and  
taking measurements as each of the nucleotides of the nucleic acid molecule passes through the channel so as to determine the sequence of the nucleic acid molecule.

(Emphasis added).

As noted above, there is no motivation to combine the *Baldarelli* and *Kool* references. In addition, as also noted above, neither *Baldarelli* nor *Kool* teach or suggest the feature highlighted in claim 67. The Office admits that *Baldarelli* does not disclose this feature. *Kool* does not cure this deficiency of *Baldarelli*. For at least the reasons previously recited, a modified nucleotide that reduces secondary structures, as recited in claim 67, is not necessarily the same as a modified

nucleotide that allows selective cleavage, as disclosed by *Kool*. Therefore, for at least this reason alone, claim 67 is not obvious in view of the combination of *Baldarelli* and *Kool*. Applicant respectfully requests that the rejection of claim 67 be withdrawn

**(d) Claims 68-100**

Because independent claim 67 is allowable over the prior art of record, its dependent claims 68-100 are allowable as a matter of law, for at least the reason that these dependent claims contain all features/steps of their respective independent claim 67. *In re Fine*, 837 F.2d 1071, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988). Additionally and notwithstanding the foregoing allowability of the independent claim 67, the dependent claims recite further features and/or combinations of features (as is apparent by examination of the claims themselves) that are patentably distinct from the prior art of record. Hence, there are other reasons why the dependent claims are allowable.

Specifically, Applicant requests that the Office point to where the features of each individual dependent claim are found in the references. There are numerous features in dependent claims 68-100 that are not discussed in the Office Action. By way of example, claim 77 recites “wherein the nucleic acid contains 2-aminoadenosine, and 2-thiothymidine.” The references, even if combined do not teach or suggest this feature. The Office Action has not established a *prima facie* case of obviousness with respect to the dependent claims 68-100. Applicant respectfully requests that the rejection of the claims be withdrawn.

(2) Claims 35 and 101 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over *Baldarelli* in view of *Kool* as applied to claims 1-34 and 67-100 above, and further in view of *Thorp et al.* (U.S. Patent No. 5,871,918, issued Feb. 16, 1999, hereinafter “*Thorp*”). Applicant respectfully traverses this rejection.

Because independent claims 1 and 67 are allowable over the prior art of record, their respective dependent claims 35 and 101 are allowable as a matter of law, for at least the reason that these dependent claims contain all features/steps of their respective independent claims 1 and 67. *In re Fine*, 837 F.2d 1071, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988). Additionally and notwithstanding the foregoing allowability of the independent claims 1 and 67, the dependent claims recite further features and/or combinations of features (as is apparent by examination of the claims themselves)

that are patentably distinct from the prior art of record. Hence, there are other reasons why the dependent claims are allowable. Applicant respectfully requests that the rejection of the claims be withdrawn.

Newly Added Claims

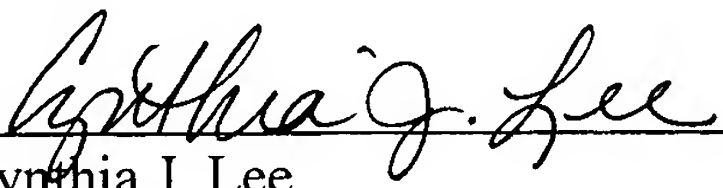
Claims 144-147 have been newly added to further define and/or clarify the scope of the invention. Applicant believes that no new matter has been added by the additional claims.



**CONCLUSION**

Applicant respectfully submits that Applicant's pending claims are in condition for allowance. Favorable reconsideration and allowance of the present application and all pending claims are hereby courteously requested. If, in the opinion of the Examiner, a telephone conference would expedite the examination of this matter, the Examiner is invited to call the undersigned attorney at (770) 933-9500.

Respectfully submitted,

  
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